Idiopathic pulmonary fibrosis is a progressive and irreversible lung condition that is difficult to diagnose and has a poor prognosis. It is characterised by progressive dyspnoea and hypoxia.

**Idiopathic pulmonary fibrosis**

**clinical features and diagnosis**

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Idiopathic pulmonary fibrosis (IPF) is one of many conditions that are grouped together under the term “interstitial lung diseases”. Despite considerable heterogeneity in the cause, presentation, treatment options and outcomes of these conditions, the interstitial lung diseases are grouped together because of similarities in clinical and radiological presentation (see Box 1, p221).

The complex and historically inconsistent terminology, multitude and relative rarity of individual subtypes of interstitial lung disease contribute to confusion in their diagnosis and description.

IPF, previously termed “cryptogenic fibrosing alveolitis” in the UK, is a chronic, progressive and fibrosing idiopathic interstitial pneumonia of unknown cause that occurs in older adults. It is irreversible and has a poor prognosis — five-year survival is around 20% and median survival after diagnosis is around two and a half years.

**Epidemiology**

IPF is the most common of the idiopathic interstitial pneumonias, accounting for around 60% of cases, and is predominantly a condition of older patients. The median age at diagnosis is 66 years (range 55–75 years) and men are more commonly affected.

There is wide variability in reported prevalence (14–43 per 100,000 population) and incidence (7–16 per 100,000 population each year) of IPF but incidence of IPF appears to be increasing; around 5,000 new cases are diagnosed in the UK each year.

**Causes**

The development of pulmonary fibrosis in IPF was previously considered to be a chronic inflammatory process; however, it is now thought that in susceptible individuals repetitive injury to the alveolar epithelium activates wound healing mechanisms rather than an inflammatory response. This results in accumulation and activation of fibroblasts and myofibroblasts in fibrotic foci that secrete an excessive amount of extracellular matrix proteins, mainly collagens, leading to scarring and destruction of the delicate lung architecture.

Although by definition IPF is a condition of unknown cause, various risk factors have been suggested.

**Cigarette smoking**

Evidence on the effects of cigarette smoking on the incidence and progression of IPF is mixed. One study suggested a 1.5–3-fold increase in the risk of IPF for patients with a smoking history compared with...
non-smokers; however, this finding has not been confirmed by other investigators.

Regardless of smoking status, IPF appears to be associated with a fivefold increased risk of developing lung cancer; it is thought that the fibrotic process creates a tumour-promoting environment in affected tissue.

Environmental exposure Environmental exposure to metal and wood dust, chemicals, farming, birds and livestock has been proposed to be linked to the development of IPF; however, convincing associations are lacking and it is worth noting that chronic hypersensitivity pneumonitis, which is associated with exposure to many antigens, can eventually progress to a similar clinical and radiological picture to that seen in patients with IPF.

Viral infection Many viruses have been suspected in the pathogenesis of IPF and researchers have suggested that chronic infection may cause lung injury and act as a co-factor promoting disease progression.

Gastro-oesophageal reflux disease Gastro-oesophageal reflux disease has been shown to be associated with IPF in patients with asymmetrical disease and treatment of the condition has been seen to be of benefit in some patients. It is assumed that ongoing aspiration of gastric contents may cause lung injury. Gastro-oesophageal reflux disease is relatively common in patients who have IPF; yet, around half of those affected are asymptomatic.

Genetics A number of candidate genes have been identified and under 5% of all cases have a familial link. The implications of these findings are unclear and there is no genetic test to identify those at risk of IPF.

Clinical features Patients who have IPF will typically develop chronic and progressive dyspnoea, occurring initially on exertion but progressing to occur at rest. Chronic cough, which is usually dry, may also be present.

Fibrosis can be detected by a fine, velcro-like chest sound and end-inspiratory crackles heard at the base of the lungs. Examples of this sound can be heard on the website www.soundsofipf.com.

Finger clubbing (see Figure 1), including the loss of the nail bed angle (also known as Schamroth’s sign), occurs in 25–50% of IPF patients and is more common in men. The cause of finger clubbing is unclear but may relate to nail bed vascular changes secondary to hypoxia. The presence and severity of finger clubbing does not appear to correlate with disease severity or prognosis of IPF. Although finger clubbing is a non-specific sign and in some patients may be idiopathic, it is associated with various serious pulmonary, cardiovascular and gastrointestinal conditions and should always be investigated.

Diagnosis Given that the prognosis and management of IPF is quite different from other interstitial lung diseases, accurate diagnosis is important. A number of interstitial lung diseases can appear similar to IPF and need to be excluded before a diagnosis of IPF can be made.

Differentiating between different interstitial lung diseases is complex: diagnosis of IPF should be made by a multidisciplinary team who have sufficient expertise in the specialism. Investigations will involve a clinical examination, pulmonary function tests, pulse oximetry and a high resolution computed tomography scan of the chest (Figure 2). Other diagnoses are then ruled out on clinical grounds, using blood testing for autoimmune or hypersensitivity conditions. In some cases, more invasive investigations, such as bronchoscopy with or without surgical lung biopsy, may be required to make a firm diagnosis.

Various pulmonary function tests are available, which provide information to assist the differentiation between pulmonary diseases, assess severity of disease and monitor response to treatment.
Spirometry
Spirometry is a non-invasive assessment that can be carried out using readily available equipment in primary care, hospital or community (see Figure 3, p224), and provides useful diagnostic and staging information for certain lung conditions.

Spirometry produces a volume-time curve showing cumulative expiratory volume (L) plotted against time (seconds). The total volume at completion of expiration is the forced vital capacity (FVC) and the volume after one second of forced expiration is the FEV₁.

For patients with normal lung function, the ratio of FEV₁ to FVC is more than 80% (ie, at least 80% of the FVC is exhaled in one second). In obstructive lung disease the FEV₁/FVC ratio is reduced with little, if any, change in the FVC; however, in restrictive lung disease the FVC is reduced to below 80% of the predicted value and the FEV₁/FVC ratio is preserved or increased. Identification of this pattern on spirometry should prompt investigation for the underlying cause.

Restrictive patterns are seen in interstitial lung disease, neuromuscular disease, obesity, ascites, cardiomegaly, pulmonary oedema, pregnancy, pleural effusion, pleural neoplasms or diffuse lung disease, pulmonary vascular disease, left-sided heart failure and anaemia.

Smokers, pregnant women and patients with pulmonary haemorrhage or polycythaemia can appear to have a larger capacity than they actually do.

Pulse oximetry
Oximetry uses a probe on the finger or earlobe to assess the degree of oxygen saturation; in the absence of hypoaxemia this is normally over 94%. For patients with severe finger clubbing, earlobe monitoring should be used.

Patients with IPF will have hypoaxemia that worsens with disease progression and on exertion. For patients with cardiovascular disease, hypoxaemia can unmask or precipitate angina.

Exercise tolerance testing with oximetry can be used to monitor patients who have IPF and other respiratory conditions. The patient walks for six minutes at a comfortable pace on level ground and is monitored continuously using oximetry. The distance covered can be used as a proxy measure of exercise tolerance, and the degree of hypoxaemia and time taken to recover is used to guide the need for initiation or titration of oxygen therapy.

A limitation of oximetry is that it does not assess the adequacy of ventilation or oxygen delivery. For example, tissue hypoxia can exist in patients with anaemia despite normal oxygen saturations.

Arterial blood gases
Measuring arterial blood gases can provide further information on ventilation and the degree of carbon dioxide retention. Patients with IPF generally have a high hypoxic respiratory drive and do not retain carbon dioxide; therefore, type II respiratory failure, which complicates the use of oxygen therapy, is not usually a problem in this group of patients.

Other investigations
Chest X-rays are non-specific and will occasionally appear normal in early IPF. If present, reticular opacity is generally most marked at the lung bases. The chest X-ray will provide information on the presence or absence of other conditions, such as cardiac failure or infection.

The term “usual interstitial pneumonia” describes the appearance of IPF on a CT scan of the chest, where the normal delicate and thin structure of the alveolar walls is replaced and thickened by fibrosis. This appears as clusters of small cysts (0.3–1.0cm in diameter) and is often described as “honeycombing”. This effect tends to be subpleural (at the base of the lungs) and paraseptal
(adjacent to the pleura on the outer boundaries of the lung). In addition to this honeycombing pattern, traction bronchiectasis — dilation of bronchi and bronchioles — may be visible.

This pattern of usual interstitial pneumonia can be similar to that seen in patients with connective tissue disease-associated-interstitial lung disease, chronic hypersensitivity pneumonitis or end-stage sarcoidosis.

For some patients, diagnosing IPF may be more complicated and will require further investigation. A bronchoscopy and bronchoalveolar lavage\(^1\) (where fluid and cells are collected for analysis) or in some cases a surgical biopsy of the affected lung tissue may be needed. Both procedures are relatively invasive and are reserved for patients for whom there is still uncertainty about a diagnosis and when the results are needed to guide treatment decisions.

**Prognosis**

The GAP index — a validated IPF staging and prognosis model — uses information on a patient’s sex, age and physiology (FVC and DL\(_{\text{CO}}\)) and predicts his or her mortality rate at one, two and three years following diagnosis with IPF (see Boxes 2 and 3); two-year mortality rates range from 11% to 62% depending on risk factors.\(^14\)

Although this is a useful clinical tool, it is widely understood that the progression of IPF is variable and unpredictable — even with seemingly similar patients. Following diagnosis, disease may progress rapidly for some patients and slowly in others. Some patients may be stable for some time but decline rapidly following an exacerbation; others may have shorter periods of stability punctuated by exacerbations.\(^15\)

Progression is monitored by serial assessments of oxygen requirements, clinical symptoms and DL\(_{\text{CO}}\). If a patient’s FVC declines by more than 10% within 12 months his or her disease is considered to be progressing rapidly. Pulmonary hypertension and right-sided heart failure with peripheral oedema can further complicate the disease course and associated symptoms, particularly in advanced IPF.

### References